PATENT SPECIFICATION

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(19)

(54) 6 β-FLUORO-PREGNANE COMPOUNDS

(71) I, GAETANO PALLADINO of Via Moscova 30, 20121 Milan, Italy, an Italian National, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

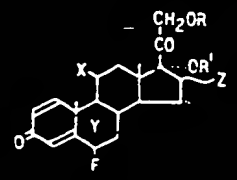
The present invention relates to a new class of 6β-fluoro-3-keto-$\Delta^{1,4}$-steroids of the pregnane series which possess valuable pharmacological properties particularly anti-inflammatory and anti-rheumatoid arthritic activity with decreased relative degree of side effects such as weight loss, sodium retention, calcium loss, adrenal and pituitary inhibition and the like, present in certain known physiologically active steroids.

From the literature it is well known to the experts in the steroid chemistry that a 3-keto-6β-fluoro-Δ^4-pregnene derivative is very instable and by epimerization it gives the corresponding 6α-fluoro-derivative.

It was now surprisingly found that 3-keto-6β-fluoro-pregnane can be stabilized in the 6β-epimer form by a suitable introduction of the $\Delta^{1,4}$-double bond system.

The resulting 6β-fluoro-$\Delta^{1,4}$-pregnadiene derivatives which are valuable pharmacologically active new products are thus object of the present invention.

According to the present invention there is provided a compound of the general formula:



(I)

in which:

R and R' are each hydrogen or an alkanoyl group having from 2 to 8 carbon atoms;

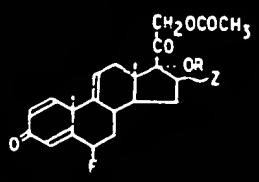
X is keto or β-hydroxy or a β-chlorine atom;

Y is a fluorine or chlorine atom but is not fluorine when X is a β-chlorine atom;

Z is hydrogen, α-hydroxyl, α-methyl or β-methyl but when X is other than a β-chlorine atom then Z is not hydrogen when R' is hydrogen; and when Z is α-hydroxyl and R' is hydrogen the corresponding 16α,17α-acetonides and 16α-alkanoates, the alkanoyl group having from 2 to 8 carbon atoms.

There will now be described a number of new interesting methods for the preparation of the new compounds of formula (I) through a series of new intermediates never described in the literature.

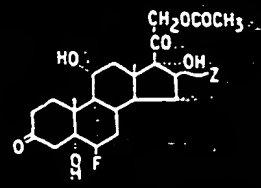
Said methods, which will be illustrated in details hereinafter are characterised in that all synthesis ways pass through a key intermediate of general formula (II):



(II)

in which R is hydrogen or an alkanoyl group having from 2 to 8 carbon atoms; Z is hydrogen, or an α- or β-methyl-group.

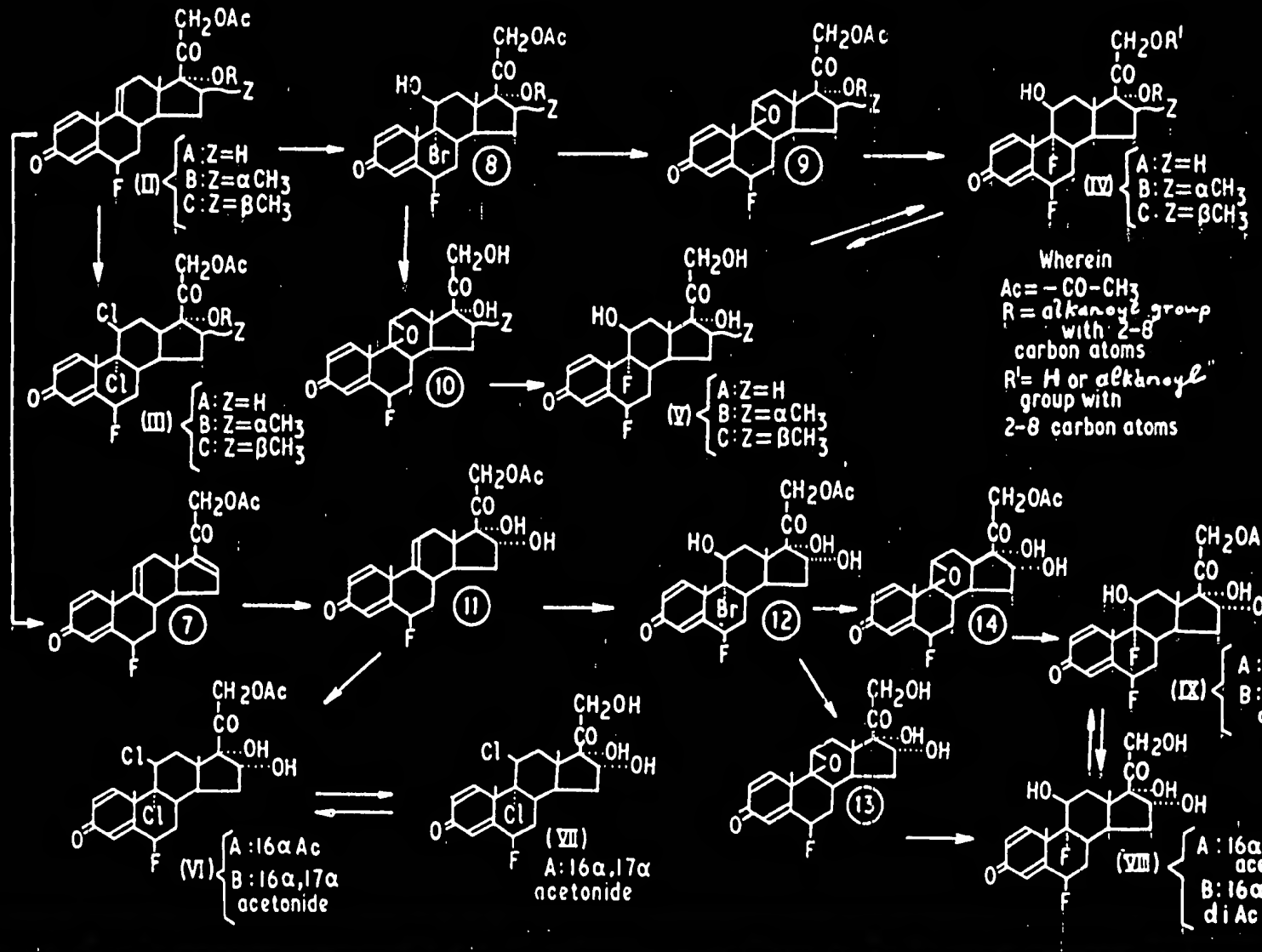
The key intermediate of formula (II) may be prepared according to the reaction Scheme N. 1 which comprises two variants, as it is clearly indicated. The starting material is represented by the formula:



(I)

in which Z is hydrogen or an α- or β-methyl-group.

This starting material may be prepared from the corresponding 5α,6α-epoxide-3-ethylenketal by reacting it with 70% aqueous hydrogen fluoride, substantially according to U.S. Patent No. 2,841,600.


(II) A: Z=H B: Z=αCH3 C: Z=βCH3
(III) A: Z=H B: Z=αCH3 C: Z=βCH3
(IV) A: Z=H B: Z=αCH3 C: Z=βCH3
(V) A: Z=H B: Z=αCH3 C: Z=βCH3
(VI) A: 16α Ac B: 16α,17α acetonide
(VII) A: 16α,17α acetonide
(VIII) A: 16α,17α acetonide B: 16α,21 di Ac
(IX) A: 16αAc B: 16α,17α acetonide
Wherein
Ac = -CO-CH3
R = alkanoyl group with 2-8 carbon atoms
R' = H or alkanoyl group with 2-8 carbon atoms

From the key-intermediate (II) according to the new methods of the present invention illustrated in the reaction Scheme N.2 a number of new products and intermediate can be prepared.

We have chosen two different systems for the numbering of all compounds reported in both Scheme No.1 and Scheme No.2: arabic numerals are used for indicating mere intermediate, whilst Roman numerals are used for indicating end-products and/or important useful intermediates.

Compound [1] dissolved in dioxan is reacted with bromine in the presence of sodium acetate to give the corresponding 2-bromo-derivative [2]. Compound [1] may be prepared from the corresponding 5α,6α-oxido-3-ethylene-ketal derivative. Compound [2] by reaction with methanesulfonyl chloride is converted into the 11α-mesyloxy-derivative [3] from which the corresponding 5α,17α-diacyl-derivative [4] is obtained by acylation with an organic acid anhydride (for example acetic or propionic anhydride) in a suitable solvent, such as ethyl acetate, and in the presence of perchloric acid. Compound [4] is then converted into the corresponding $\Delta^{1,4,9(11)}$-pregnatriene i.e. into the above mentioned key-intermediate (II). This conversion may be effected by treatment at 110—120° C. with lithium chloride and pyridine in dimethylformamide. Alternatively compound [4] may be obtained also from compound [1] according to the reaction sequence [1]→[5]→[6]→[4] of Scheme N.1.

Compound [1] by reaction with methanesulfonyl chloride is converted into the 11α-mesyloxy-derivative [5], which is acylated with an organic acid anhydride in a suitable solvent such as ethyl acetate and in the presence of perchloric acid to give the corresponding 6β-fluoro-3,5α,17α-triacyloxy-11α-mesyloxy-21-acetoxy-pregn-2-en-20-one [6] which may be converted into the 2-bromo-derivated by reaction with bromine in dioxane or with dibromo-dimethyl-hydantoin in tetrahydrofuran. The key-intermediate (II) is then converted into the corresponding 9α-bromo-11β-hydroxy-compound [8] according to the known procedures, for instance by reaction with N-bromo-acetamide or N-bromo-succinimide. From compound [8] *either* the corresponding 9β,11β-oxido-17α,21-diol diacylate [9] *or* 9β,11β-oxido-17α,21-diol [10] may be prepared.

Compound [9] is reacted with 70% hydrogen fluoride at a temperature between −15° and −5° C. to give the corresponding 9α-fluoro-11β-hydroxy-17α,21-diacylate (IV). Alternatively under the same conditions compound [10] gives the corresponding 9α-fluoro-11β,17α,21-triol-derivative (V). Compound (V) may be obtained on alkaline hydrolysis of (IV) with potassium hydroxide in methanol and in nitrogen atmosphere. Compound (IV) may be prepared through the 17α,21-ortho-esters of (V), on hydrolysis of said ortho-esters to 17α-acyl-esters and by subsequent acylation in the 21-position.

By reacting compound (II) dissolved in acetic acid with N-chloro-succinimide in the presence of lithium chloride, the corresponding 9α,11β-dichloro-derivative (III) may be obtained.

By reacting compound (II), in which Z is hydrogen, dissolved in dimethyl formamide with potassium acetate the corresponding Δ^{16}-derivative [7] may be obtained. Treatment of the latter compound dissolved in aqueous acetone with potassium permanganate in the presence of formic acid at −10° C. results in the corresponding 16α,17α-dihydroxy-derivative [11]. Reacting the latter compound in acetic acid with N-chlorosuccinimide in the presence of lithium chloride forms the corresponding 9α,11β-dichloro-derivative (VI).

By acylating (VI) in pyridine with an organic acid anhydride the 16α-acyl-derivative is produced (VI A).

Treatment of (VI) with acetone and perchloric acid affords the corresponding 16α,17α-acetonide (VI B).

On hydrolysing compound (VI) in aqueous methanol with potassium carbonate under nitrogen atmosphere the corresponding 21-alcohol (VII) may be obtained.

On reacting compound (VII) with acetone in the presence of perchloric acid the corresponding 16α,17α-acetonide may be obtained.

The "1,4,9(11)-triene" [11] may be converted into the corresponding 9α-bromo-11β-hydroxy-derivative [12] from which either the 9β,11β-oxido-21-ol [13] or the 9β,11β-oxido-21-acetate [14] may be prepared. On reacting either compound [13] or compound [14] with 70% aqueous hydrogen fluoride at −10° C. the corresponding compound (VIII) and respectively compound (IX) may be prepared.

On hydrolysing compound (IX) in methanol with potassium hydroxide under nitrogen atmosphere compound (VIII) may be obtained.

Reacting either compound (VIII) or compound (IX) with acetone in the presence of perchloric acid [illegible]

By acylating compound (IX) and respectively (VIII) in pyridine with an organic acid anhydride, the corresponding 16α-acyl-derivative (IX A) and respectively the corresponding 16α,21-diacyl-derivative (VIII B) may be prepared.

Treatment of 9β,11β-oxido-derivatives [9], [10], [13] and [14] with concentrated hydrochloric acid (36%) at 0° C. affords the corresponding 9α-chloro-11β-hydroxy-derivatives.

The oxidation of the 9α-halo-11β-hydroxy-steroids (see compounds (IV) (IX A) and (IX B)) to the corresponding keto compound (where desired) may be effected by the conventional oxidizing procedures, e.g. CrO_3 in acetic acid.

The following Examples 9, 10, 11, 16, 17, 18 and 19 are in accordance with the present invention, the remaining examples being given by way of information.

EXAMPLE 1.

2-Bromo-6β-fluoro-pregnane-5α,11α,17α,21-tetrol-3,20-dione 21-acetate (Compound [2], Z=H).

To a suspension of 1g of 6β-fluoro-pregnane-5α,11α,17α,21-tetrol-3,20-dione 21-acetate and of 0.5g of anhydrous sodium acetate in 15 ml. of dioxan 0.5g of bromine are added at 25—28° C. with stirring. After 5 minutes the reaction mixture is poured onto 100 ml of cold distilled water. The precipitate is filtered, dried, and re-crystallized from chloroform-methanol.

Yield 0.8g of product. (Compound [2] Z=H).

IR (in Nujol (Registered Trade Mark)) 3520, 3420, 3230, 1760,1720, 1225 cm^{-1}.

EXAMPLE 2.

2-Bromo-6β-fluoro-pregnane-5α,11α,17α,21-tetrol-3,20-dione 11α-mesylate-21-acetate (Compound [3] Z=H).

To a solution of 5g of compound [2], Z=H in 25ml. of pyridine cooled to −10° C., 3 ml of methanesulfonyl chloride are added drop-wise with stirring. Stirring is continued for 30 minutes whereupon the reaction mixture is poured onto 250 ml of cold water. The pH of the resulting suspension is adjusted to 3.5 with 10% aqueous dilute sulfuric acid. The suspension is then filtered and the crude compound [3], Z=H is dried. Yield 5.5g.

EXAMPLE 3.

2-Bromo-6β-fluoro-pregnane-11α-mesyloxy-5α,17α,21-triacetyloxy-3,20-dione (compound [4] Z=H R=Ac).

1g of [3], Z=H is dissolved in a mixture of 44 ml. of ethyl acetate, 7.5 ml of acetic anhydride and 0.05 ml of 70% perchloric acid. The reaction mixture is kept with stirring at room temperature for 30 minutes then it is poured into a separating funnel containing cold solution of 13g of sodium bicarbonate in 60 ml of water. The whole mixture is thoroughly shaked and allowed to separate.

The organic layer is concentrated "in vacuo" to a semi-solid residue. This is then triturated with ethyl ether and the solid is filtered and washed with the same solvent. Yield 1g.

% Br calculated 11.7%:

found 12.1% UV-Spectrum λ_{max}^{MeOH} 285 mμ.

EXAMPLE 4.

6β-fluoro-2-pregnene-11α-mesyloxy-5α,17α,21-triacetyloxy-20-one-3-enol acetate (compound [6], Z=H, R=Ac).

Starting from compound [1] there is obtained compound [5], Z=H by using the same procedure as described in EXAMPLE 2. Compound [6], Z=H is obtained from [5] by using the same procedure as described in EXAMPLE 3.

EXAMPLE 5.

2-Bromo-6β-fluoro-pregnane-11α-mesyloxy-5α,17α,21-triacetyloxy-3,20-dione (compound [4] from [6] Z=H, R=Ac).

To a solution of 1g of [6] in 10 ml of tetrahydrofuran 0.1 ml of 35% perchloric acid and 0.5g of dibromo-dimethyl-hydantoin are added with stirring.

After 1 hour at room temperature the reaction mixture is slowly poured in 100 ml of an aqueous diluted solution of sodium sulfite so as to eliminate the excess of bromine. The suspension is then filtered, the crude product is collected and dried. Yield 1.05g of the desired product with the same characteristic of that obtained from compound [3] as described in EXAMPLE 3.

EXAMPLE 6.

6β-fluoro-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17,21-diacetate (compound II Z=H, R=Ac).

To a suspension of 5g of 2-bromo-6β-fluoro-pregnane-11α-mesyloxy-5α,17α,21-triacetyloxy-3,20-dione in 50 ml of dimethyl formamide 5g of lithium chloride and 0.5 ml of pyridine are added with stirring. While bubbling nitrogen in the reaction mixture this is warmed up to 110°—120° C. and kept for 40 minutes. Upon cooling to 20° C. the reaction mixture is poured little by little in 500 ml of cold water. The resulting suspension is filtered, the crude product is collected and dried. Yield 3.5g.

The crude product crystallises readily from methanol giving 2.5g of pure product having the following properties:

UV-Spectrum λ_{max}^{MeOH} 239—240 mμ $E_{1\,cm}^{1\%}$ 338

IR-Spectrum 1740 1675 1640 1235 cm^{-1}.

analysis calculated for $C_{23}H_{29}FO_6$ M.W. 444.5

C 67.5% H 6.55%; found 66.8% H 6.42%

The N.M.R. analysis confirms the steric configuration β of the fluorine atom in position 6.

EXAMPLE 7.

6β-fluoro-9β,11β-oxido-1,4-pregnadiene-17α,21-diol-3,20-dione 17,21-diacetate (compound [9] Z=H, R=Ac).

10g of compound (II A) (Z=H; R=Ac), obtained according to EXAMPLE 6, are suspended in 100 ml of tetrahydrofuran. To the resulting suspension kept at +10° C. with stirring 5g of N-bromo-acetamide and 10 ml of 7% aqueous perchloric acid are added, and the mixture is kept under gently stirring for 1 hour. Then the excess of bromine is removed by addition of an aqueous solution of sodium sulfite, and the whole mass is slowly poured into 1 litre of cold water with stirring. The corresponding 9α-bromo-11β-hydroxy-derivative, thus formed, compound [8], is filtered and the crude intermediate is suspended in 150 ml of acetone containing 15g of potassium acetate and refluxed for 1 hour.

The reaction mixture is then poured in cold water. After filtration and drying 4g of crude product are obtained. (Compound [9] Z=H; R=Ac).

UV-Spectrum: λ_{max}^{MeOH} 248—249 mμ $E_{1\,cm}^{1\%}$ =330

EXAMPLE 8.

6β-fluoro-9β,11β-oxido-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione (compound [10], Z=αCH$_3$).

To a solution of 6β-fluoro-9α-bromo-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione prepared from 10 g of compound (II B) (Z=αCH$_3$, R=Ac), according to the same procedure of EXAMPLE 7, in 100 ml of methanol is added an aqueous solution of 5g of potassium carbonate. The mixture is kept at 15—20° C. with stirring for 1 hour. The excess of potassium carbonate is neutralized with acetic acid and the reaction mixture is slowly poured in 1 litre of cold water with stirring. The crude product is filtered, washed with water and dried. Yield 3.2g. Upon a crystallization from acetone 2.8g of pure product are obtained.

IR-Spectrum (Nujol) maximum at 3400—1715—1660—1615 cm^{-1}.

EXAMPLE 9.

6β,9α-difluoro-prednisolone 17α,21-diacetate (compound IV A Z=H, R=Ac).

To 10 ml of 70% aqueous hydrogen fluoride cooled to −10° C. 2g of 6β-fluoro-9β,11β-oxido-1,4-pregnadiene-17α,21-diol-3,20-dione 17,21-diacetate, obtained according to EXAMPLE 7, are slowly added in a polyethylene vessel with a magnetic stirrer. After 30 minutes the reaction mixture is poured with precaution in cold aqueous ammonia.

The product is filtered, washed with water and dried. 2g of crude product are obtained; a crystallization from methanol gives 1.3g of the desired pure product.

UV-Spectrum λ_{max}^{MeOH} 238 mμ $E_{1\,cm}^{1\%}$ 310

IR-Spectrum λ_{max}^{nujol} 3400—1730—1665—1630—1235 cm^{-1}.

$[\alpha]_D = -14.2°$ (C=0.5 in $HCCl_3$)

The NMR spectrum confirms the steric configuration β of the fluorine atom in the position 6.

EXAMPLE 10.

6β,9α-difluoro-16α-methyl-prednisolone (compound V B, Z=αCH_3).

By starting from the 9β,11β-epoxido-derivative [10], prepared according to EXAMPLE 8 and by operating according to EXAMPLE 9, 6β,9α-difluoro-16α-methyl-prednisolone is obtained.

UV-Spectrum λ_{max}^{MeOH} =239 mμ; $E_{1\,cm}^{1\%}$ =399; $[\alpha]_D$=+5.2° (dioxane).

EXAMPLE 11.

6β,9α-difluoro-16α-methyl-prednisolone 21-pivalate.
(compound IV B Z=αCH_3; R=—CO—C$(CH_3)_3$).

To a solution of 1g of 6β,9α-difluoro-16α-methyl-prednisolone in 10 ml of pyridine 0.7 ml of pivaloyl chloride are added. The reaction mixture is kept at 10—15° C. for 2 hours, then it is poured in 100 ml of cold water containing 2.5 ml of 96% sulfuric acid. The resulting suspension is filtered, washed with water and dried. The crude product is recrystallised from ethyl acetate—ethyl ether.

0.6g of 6β,9α-difluoro-16α-methyl-prednisolone 21-pivalate are obtained.

UV-Spectrum λ_{max}^{MeOH} =239 $E_{1\,cm}^{1\%}$ 314

IR-Spectrum λ_{max}^{Nujol} 3460—3360—1735—1715—1670—1630 cm^{-1}.

$[\alpha]_D$=+23° (c=1 dioxan).

EXAMPLE 12.

6β-fluoro-1,4,9(11), 16-pregnatetraen-21-ol-3,20-dione 21-acetate (compound [7]).

To a suspension of 25 g of anhydrous potassium acetate in 300 ml of dimethylformamide, 5 g of 6β-fluoro-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 17,21-diacetate (compound (II) Z=H, R=Ac) are added. The suspension is heated to 110—120° C. under nitrogen atmosphere with stirring.

The reaction mixture is kept under these conditions for 4 hours, then it is cooled to 20° C. and it is poured little by little in 3 litres of cold water with stirring. The product is filtered, washed with water and dried. 3.5 of compound [7] are obtained.

UV-Spectrum λ_{max}^{MeOH} =240 mμ $E_{1\,cm}^{1\%}$ =646

IR-Spectrum λ_{max}^{nujol} 1740—1675—1635—1585—1230—1240 cm^{-1}.

EXAMPLE 13.

6β-fluoro-1,4,9(11)-pregnatriene-16α,17α,21-triol-3,20-dione 21acetate
(compound [11]).

To a solution of 5g of compound [7] prepared according to EXAMPLE 12, in 200 ml of pure acetone and 1.2 ml of 99% formic acid cooled to −10° C. a solution of 2.3g of potassium permanganate in 100 ml of 80% aqueous acetone with stirring is added.

After a few minutes a 10% aqueous solution of sodium bisulfite is added dropwise to remove the excess of permanganate. The precipitated salts are filtered, the filtrate is concentrated "in vacuo" to remove the solvent. The resulting aqueous suspension is filtered. Yield 3.7 of the desired compound [11].

UV-Spectrum λ_{max}^{MeOH} 240 mμ; $E_{1\,cm}^{1\%}$ =390

IR-Spectrum λ_{max}^{Nujol} 3450—3350—1750—1730—1665—1625—1230 cm^{-1}.

EXAMPLE 14.

6β-fluoro-9β,11β-oxido-1,4-pregnadiene-16α,17α,21-triol-3,20-dione (compound [13]).

By using compound [11]—see EXAMPLE 13—as starting material and by operating as described in EXAMPLE 8 through the "bromhydrine" [12] the desired compound [13] is obtained.

UV-Spectrum λ_{max}^{MeOH} 249 mμ; $E_{1\,cm}^{1\%}$ 398.

IR-Spectrum λ_{max}^{Nujol} 3440—1715—1670—1635 cm^{-1}.

EXAMPLE 15.

6β-fluoro-9β,11β-oxido-1,4-pregnadiene-16α,17α,21-triol-3,20-dione 21-acetate (compound [14]).

By using compound [11] as starting material and by operating as described in EXAMPLE 7 the desired compound [14] is obtained.

IR-Spectrum λ_{max}^{Nujol} 3350—1720—1665—1625—1235 cm^{-1}.

EXAMPLE 16.

6β,9α-difluoro-16α-hydroxy-prednisolone (compound VIII).

By using compound 13—see EXAMPLE 14—as starting material and by operating as described in EXAMPLE 9 the desired compound (VIII) is obtained.

UV-Spectrum λ_{max}^{MeOH} =238 $E_{1\,cm}^{1\%}$ =366

IR-Spectrum λ_{max}^{Nujol} 3400—3300—1710—1668—1630 cm^{-1}.

EXAMPLE 17.

6β,9α-difluoro-16α-hydroxy-prednisolone 16α,17α-acetonide 21-acetate (compound IX B).

To a suspension of 500 mg of Compound VIII in 75 ml of acetone is added 0.05 ml of 72% perchloric acid and the mixture agitated at room temperature for three hours. During this period the crystals gradually dissolve and the clear solution is neutralized with dilute sodium bicarbonate and the acetone removed in vacuo. The resulting crystalline suspension is filtered and the crystals washed with water. The crude dried material is acetylated with acetic anhydride in pyridine. The 21-acetate thus obtained has the following characteristics:

UV-Spectrum λ_{max}^{MeOH} 239 mμ $E_{1\,cm}^{1\%}$ =309

$[\alpha]_D$=+38.3 (c=1 dioxan).

EXAMPLE 18.

6β-fluoro-9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 17,21-diacetate (compound III A).

To a solution of 5 g of Compound II A (R=acetyl) and of 20 g of lithium chloride in 200 ml of glacial acetic acid there is added 2.5 g of N-chlorosuccinimide with stirring. The reaction mixture is kept at 15—20° C. under stirring for a further three hours, then it is poured into cold water. The precipitate is filtered, washed with water and dried. Upon crystallization of the crude product from aqueous acetone 2.5 g of Compound III A (R=acetyl) having the following characteristics are obtained:

UV-Spectrum λ_{max}^{MeOH} 237—238 mμ; $E_{1\,cm}^{1\%}$ =304.

$[\alpha]_D$=+309.9 (c=1 dioxan).

EXAMPLE 19.

6β-fluoro-9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17,21-diacetate (compound III B).

By starting from compound II B (R=acetyl) and by operating as indicated in EXAMPLE 18, Compound III B (R=acetyl) is obtained, having the following characteristics:

UV-Spectrum 237—238 mμ; $E_{1\,cm}^{1\%}$ =284

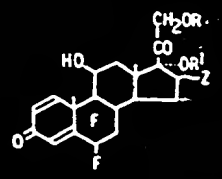
$[\alpha]_D$=+27° (c=1 dioxan).

Intermediates useful in the preparation of the compounds of the present invention form the subject matter of my co-pending application No. 42978/77 (Serial No. 1,504,295).

The present invention also relates to an anti-inflammatory composition comprising a compound of the present invention together with a pharmacologically acceptable carrier.

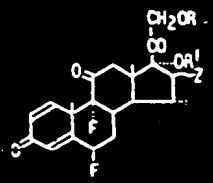
WHAT I CLAIM IS:—

1. A 6β,9α-difluoro-prednisolone derivative of structure:



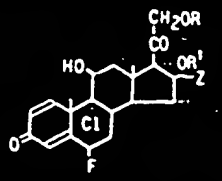
wherein R and R′ are each hydrogen or an alkanoyl group having from 2 to 8 carbon atoms, and Z is hydrogen, α-methyl, β-methyl, or α-hydroxy but is not hydrogen when R′ is hydrogen; and, when Z is α-hydroxy and R′ is hydrogen; the corresponding 16α,17α-acetonides and the 16α-alkanoates, the alkanoyl group having from 2 to 8 carbon atoms.

2. A 6β,9α-difluoro-prednisone derivative of structure:



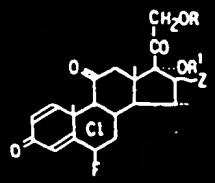
wherein R, R′ and Z have the same meaning as in claim 1, and when Z is α-hydroxy and R′ is hydrogen the corresponding 16α,17α-acetonides and the 16α-alkanoates, the alkanoyl group having from 2 to 8 carbon atoms.

3. A 6β-fluoro-9α-chloro-prednisolone derivative of the structure:



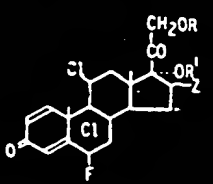
wherein R, R′ and Z have the same meaning as in claim 1, and when Z is α-hydroxy and R′ is hydrogen the corresponding 16α,17α-acetonides and the 16α-alkanoates, the alkanoyl group having from 2 to 8 carbon atoms.

4. A 6β-fluoro-9α-chloro-prednisone derivative of the structure:



where R, R′ and Z have the same meaning as in claim 1 and when Z is α-hydroxy and R′ is hydrogen the corresponding 16α,17α-acetonides and the 16α-alkanoates, the alkanoyl group having from 2 to 8 carbon atoms.

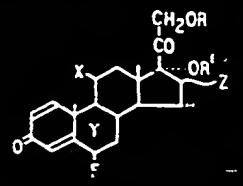
5. A 6β-fluoro-9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione-17,21-diacylate of structure:



wherein R and R′ are each hydrogen or an alkanoyl group having from 2 to 8 carbon

atoms; and Z is hydrogen, α-methyl, β-methyl or α-hydroxy; and when Z is α-hydroxy and R′ is hydrogen, the corresponding 16α,17α-acetonides and the 16α-alkanoates, the alkanoyl group having from 2 to 8 carbon atoms.

6. A 6β-fluoro-1,4-pregnadiene-17α,21-diol-3,20-dione-derivative of the structure:



(I)

in which:

R and R′ are each hydrogen or an alkanoyl group having from 2 to 8 carbon atoms;

X is keto or β-hydroxyl or a β-chlorine atom;

Y is a fluorine or chlorine atom but is not fluorine when X is a β-chlorine atom;

Z is hydrogen, α-hydroxyl, α-methyl or β-methyl but when X is other than a β-chlorine atom then Z is not hydrogen when R′ is hydrogen and when Z is a α-hydroxyl and R′ is hydrogen the corresponding 16α,17α-acetonides and 16α-alkanoates, the alkanoyl group having from 2 to 8 carbon atoms.

7. 6β,9α-difluoro-prednisolone 17α,21-diacetate.

8. 6β,9α-difluoro-16α-methyl-prednisolone.

9. 6β,9α-difluoro-16α-methyl-prednisolone 21-pivalate.

10. 6β,9α-difluoro-16α-hydroxy-prednisolone.

11. 6β,9α-difluoro-16α-hydroxy-prednisolone 16α,17α-acetonide 21-acetate.

12. 6β-fluoro-9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 17,21-di-acetate.

13. 6β-fluoro-9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 17,21-diacetate

14. A compound as claimed in any preceding claim, substantially as hereinbefore described.

15. An anti-inflammatory composition comprising a compound as claimed in any preceding claim, together with a pharmacologically-acceptable carrier.

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